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REMARKS

Claims 1, 4, 6-8, 10-14 and 19 are pending in the application. All claims stand rejected.

The only outstanding issue in this case is whether the claims are patentable over the teachings of JP '279 in view of JP '882.

The claims are directed to a drug composition comprising lecithin-modified superoxide dismutase (PC-SOD) and sucrose. Sucrose is added to the composition to stabilize PC-SOD against degradation of the lecithin moieties.

The JP '279 reference is relied on to show that PC-SOD was known. The Examiner has mistakenly relied upon the JP '882 reference to show that "addition of sucrose to the freeze-drying mixture of SOD avoids the denaturation problems accompanying the SOD freeze-drying process"

The JP '279 document is relevant only to the extent that it discloses PC-SOD, and its potential uses and advantages in pharmacological therapeutic treatments. Applicants are not claiming PC-SOD, its uses, or its advantages. Applicants are claiming a composition that overcomes problems associated with degradation of the phosphatidyl choline (PC) moieties surrounding the SOD.

The prior art (JP '882) teaches that dimerization of SOD is a problem that must be avoided to prevent allergenic effects. The prior art teaches that there is no problem with denaturation of SOD during freezing and thawing or freeze-drying, unless a denaturant is added, and that sucrose (among numerous other compounds) may be used to prevent dimerization of SOD without also causing denaturation, as is the case with certain aldose monosaccharides.

None of the prior art references, including the JP '882 translation, teach or suggest that either human PC-SOD or human SOD undergo denaturation during a freeze-drying process, unless a denaturant is added to the composition. The JP '882 document states there is "[n]o decrease in the enzymatic action of human SOD . . . when this protein is subjected to freezing and thawing or freezing-drying processes" and provides several examples showing that there is no denaturation in the absence of a denaturant. The Examiner has refuted these facts

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because the JP '882 translation states that "even with the combination of aldose monosaccharides such as galactose, arabinose, glucose, and the like to human SOD prior to freeze-drying, analysis by anion-exchange chromatography reveals denaturation (Comparative Example 3)." This is not a teaching that there is any inherent need to stabilize SOD against denaturation during freeze-drying processes. The reference is teaching that aldose monosaccharides prevent dimerization of SOD and the resulting allergenic side effects caused by the SOD dimer, but also cause undesirable denaturation, which does not occur in the complete absence of anti-dimerization stabilizers. This is confirmed by the examples. Comparative Example 2 shows that analysis by anion-exchange chromatography "did not reveal any denaturation of human SOD" during freeze-drying without a stabilizer or other additive. However, gel permeation analysis revealed a 0.45% quantity of by-product at 79 KD (SOD dimer). Comparative Examples 3-5 show that the use of aldose monosaccharides, including arabinose, glucose, and galactose, all substantially reduce dimerization as compared with a similar composition that does not contain any stabilizer, but that the aldose monosaccharides that were tested all caused denaturation. Thus, the data show that denaturation of SOD does not occur during freezing/thawing and/or freeze-drying of compositions containing SOD unless a denaturant is added, such as an aldose monosaccharide. The JP '882 document is teaching that a stabilizer is only required to prevent SOD dimerization and associated undesirable allergenic effects.

There is nothing on the record to suggest that PC-SOD dimerizes or forms allergenic materials during freeze-drying and/or freezing/thawing operations. Further, there is evidence on the record showing that SOD and PC-SOD are substantially different materials that behave substantially differently. PC-SOD is derived from SOD by reacting functional groups on the SOD with phosphatidyl choline, thereby eliminating reactive sites responsible for dimerization of unmodified SOD. Further, it is well recognized by those having ordinary skill in the art that such modifications also create steric and conformational effects that would cause PC-SOD to behave differently from SOD. Absent evidence to the contrary, those having ordinary skill in the art would not expect PC-SOD to undergo dimerization reactions of the type that cause the known allergenic problems with SOD during freeze-drying and/or freeze/thawing

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processes. Further, U.S. Patent No. 5,762,929 (made of record in the accompanying Information Disclosure Statement) discloses (column 1, lines 58-62) that PC-SOD provides a desirable therapeutic effect "without adverse effect such as antigenicity." Within the context of a protein or derivatized protein, the absence of adverse antigenicity equates to an absence of allergenic side effects. Accordingly, the prior art of record teaches that the allergenic side effects caused by dimerization of SOD are not present with PC-SOD. When one having ordinary skill in the art combines this teaching in the prior art with the teachings of the JP '882 translation (i.e., that a stabilizer is needed to prevent dimerization of SOD and thereby prevent allergenic side effects), one having ordinary skill in the art would not be motivated to add a stabilizer to a composition containing PC-SOD. A reference teaching the use of an additive that prevents dimerization of SOD without also causing denaturation does not provide motivation for adding a stabilizer to a composition containing PC-SOD, which is not known to exhibit either dimerization or denaturation problems.

The rejection under 35 U.S.C. §103 is based on the following allegations:

1. The '882 translation teaches that a stabilizer is needed to prevent denaturation of SOD.
2. There is not any evidence of record showing that dimerization and associated allergenic side effects are not a problem with PC-SOD.
3. "[I]t is a scientific fact that the protein portion of PC-SOD is subject to degradation by proteases, and one of ordinary skill would recognize this."

Applicants have shown that the JP '882 translation states and provides data showing that a stabilizer is only needed during freezing/thawing or freezing-drying of SOD to prevent dimerization, and that denaturation is not an issue during freeze-drying and/or freeze/thawing of compositions containing SOD, unless a denaturant is added. Further, there is no suggestion in the prior art that sucrose is an anti-denaturant for SOD. To the contrary, the prior art only shows that sucrose prevents dimerization of SOD, without causing denaturation of SOD.

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Applicants have made of record prior art showing that the allergenic side effect caused by dimerization of SOD is not a problem with PC-SOD (see U.S. Patent No. 5,762,929, column 1, lines 58-62). Addition of a stabilizer to prevent SOD dimerization does not provide motivation for adding a stabilizer to PC-SOD, since one having ordinary skill in the art would not be motivated to add a dimerization stabilizer to a composition that does not exhibit problems with dimerization.

Finally, there is not any evidence of the existence of a protease that would be capable of causing denaturation of lecithin-modified SOD, or that those having ordinary skill in the art would expect that such a protease exists. Regardless, such speculation about the existence of proteases that might be capable of causing denaturation of PC-SOD is completely irrelevant to the claimed invention. The JP '882 translation repeatedly states and provides data showing that denaturation does not occur in the absence of a denaturant during freeze/thawing and/or freeze-drying of SOD.

Because the prior art of record teaches that it is not necessary to add a stabilizer to SOD to prevent denaturation, and because there is not any teaching in the prior art that it is necessary to prevent either denaturation or dimerization of PC-SOD, there is an absence of motivation for adding sucrose to a composition containing PC-SOD. For these reasons, a withdrawal of the rejection and issuance of a Notice of Allowance are appropriate.

Respectfully submitted,

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Date

GJE/dac



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